

### **AMENDMENTS TO THE CLAIMS**

1. **(Previously Presented)** A method of determining whether an individual has a predisposition to migraine comprising

obtaining a biological sample from said individual, said sample comprising at least one nucleic acid from said individual that comprises a nucleotide sequence of at least a fragment of a female steroid sex hormone receptor gene, and

determining whether there is a polymorphism in said nucleotide sequence, wherein the presence of the polymorphism in said nucleotide sequence indicates that said individual has an increased predisposition to migraine compared to an individual without the polymorphism.

2. **(Previously Presented)** The method of Claim 1, wherein said nucleotide sequence is of at least a fragment of exon 8 of a human estrogen receptor (ESR1) gene that encodes codon 594 of an estrogen receptor protein.

3. **(Previously Presented)** The method of Claim 2, wherein the polymorphism is a guanine to adenine change at nucleotide 2014 of the ESR1 gene.

4. **(Previously Presented)** The method of Claim 1, wherein said nucleotide sequence is of at least a fragment of a progesterone receptor gene, wherein said nucleotide sequence comprises a 306 base pair insertion in intron 7 of said progesterone receptor gene.

5. **(Previously Presented)** The method of Claim 3, wherein the polymorphism is detected as a restriction fragment length polymorphism.

6. **(Previously Presented)** The method of Claim 4, wherein said 306 base pair insertion is detected according to size.

7. **(Previously Presented)** The method of Claim 1, wherein said sample comprises at least two nucleic acids from said individual, a first nucleic acid comprising a nucleotide sequence of at least a fragment of exon 8 of a human ESR1 gene and a second nucleic acid comprising a nucleotide sequence of at least a fragment of intron 7 of a human progesterone receptor gene.

8. **(Previously Presented)** The method of Claim 7, wherein the first nucleic acid comprises a polymorphism that is a guanine to adenine change at nucleotide 2014 of the human ESR1 gene and/or the second nucleic acid comprises a 306 base pair insertion in intron 7 of the human progesterone receptor gene.

9. **(Previously Presented)** A method of determining whether an individual has a predisposition to migraine comprising

(a) obtaining a biological sample from said individual, said sample comprising

(i) a first nucleic acid that comprises a first nucleotide sequence of at least a fragment of a first female steroid sex hormone receptor gene; and

(ii) a second nucleic acid that comprises a second nucleotide sequence of at least a fragment of a second female steroid sex hormone receptor gene; and

(b) determining whether there is a polymorphism in each of said first and second nucleotide sequences,

wherein the presence of a polymorphism in said first nucleotide sequence of (i) and in said second nucleotide sequence of (ii) indicates that said individual has an increased predisposition to migraine compared to that of an individual having a polymorphism in (i) or (ii) alone.

10. **(Previously Presented)** The method of Claim 9, wherein said first nucleotide sequence in (i) is of at least a fragment of exon 8 of a human estrogen receptor (ESR1) gene that encodes codon 594 of an estrogen receptor protein.

11. **(Previously Presented)** The method of Claim 10, wherein the polymorphism is a guanine to adenine change at nucleotide 2014 of the ESR1 gene.

12. **(Previously Presented)** The method of Claim 9, wherein said second nucleotide sequence in (ii) is of at least a fragment of a progesterone receptor gene, wherein said nucleotide sequence comprises a 306 base pair insertion in intron 7 of said progesterone receptor gene.

13. **(Previously Presented)** The method of any preceding claim, wherein migraine is migraine with aura or migraine without aura.

14. **(Currently Amended)** ~~A-~~The method of Claim 1, wherein the determining comprises amplifying said nucleic acid with kit for identifying a predisposition to migraine, said kit comprising one or more primers for nucleic acid sequence amplification of said at least a fragment of a said female sex steroid hormone receptor gene, and instructions to determine whether there is a polymorphism in said fragment.

15. **(Currently Amended)** The ~~kit-method~~ of Claim 14, ~~which comprises wherein said one or more primers comprise~~ primers for nucleic acid sequence amplification of at least a fragment of exon 8 of a human ESR1 gene that encodes codon 594 of an estrogen receptor protein.

16. **(Currently Amended)** The ~~kit-method~~ of Claim 15, wherein the ~~kit determining~~ further comprises digesting amplification products with a *BtgI* restriction endonuclease.

17. **(Currently Amended)** The ~~kit-method~~ of Claim 14, wherein said one or more primers comprise ~~which comprises~~ primers for nucleic acid sequence amplification of at least a fragment of intron 7 of a human progesterone receptor gene.

18. **(Currently Amended)** ~~A kit for identifying a predisposition to migraine, said~~ The method of Claim 9, wherein the determining comprising amplifying with kit comprising one or more primers for nucleic acid sequence amplification of:

(i) ~~a the~~ first nucleic acid that comprises ~~a the~~ nucleotide sequence of the at least a fragment of ~~a the~~ first female steroid sex hormone receptor gene; and

(ii) ~~a the~~ second nucleic acid that comprises ~~a the~~ nucleotide sequence of the at least a fragment of ~~a the~~ second female steroid sex hormone receptor gene.

19. **(Currently Amended)** The ~~kit-method~~ of Claim 18, wherein said one or more primers comprise ~~which comprises~~:

(a) primers for nucleic acid sequence amplification of at least a fragment of exon 8 of a human ESR1 gene that encodes codon 594 of an estrogen receptor protein; and

(b) primers for nucleic acid sequence amplification of at least a fragment of intron 7 of a human progesterone receptor gene.

20. **(Currently Amended)** The ~~kit-method~~ of Claim 19, wherein ~~determining the kit~~ further comprises digesting amplification products with a *BtgI* restriction endonuclease.

21. **(Withdrawn)** A method of determining whether an individual has a predisposition to migraine comprising

isolating a progesterone receptor protein, or fragment thereof, and

determining whether said individual has a human progesterone receptor protein polymorphism,

wherein the presence of said polymorphism indicates an increased predisposition to migraine compared to an individual without the polymorphism.

Application No.: 10/571,879  
Filing Date: January 29, 2007

22. **(Withdrawn)** The method of Claim 21, wherein the progesterone receptor protein is detected according to an altered expression level that indicates said individual has a 306 base pair insertion in the human progesterone receptor gene.
23. **(Previously Presented)** The method of Claim 1, wherein the determining step comprises amplification of said nucleic acid.
24. **(Previously Presented)** The method of Claim 1, wherein the determining step comprises digesting said nucleic acid.
25. **(Previously Presented)** The method of Claim 1, wherein the determining step comprises gel electrophoresis of said nucleic acid.